

## **REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

### **I. Status of the Claims**

Claim 2 has been amended for greater clarity. Claim 12 has been amended to replace trademarks with the corresponding chemical names.

Applicants acknowledge the finality of this Office Action. Because the amendments to the claims do not add new matter and do not require additional search, and they either place the application in condition for allowance or at least in better condition for appeal Applicants respectfully request entry of this amendment.

Upon entry, claims 1-10, 13-17 and 56-57 will be under examination, with claims 11-12 and 18-55 withdrawn.

### **II. Species Election**

The Examiner requests withdrawal of claims 11 and 12 based on the species election of non-ionic surface stabilizer. Without acquiescing to the stated basis, Applicants withdraw claims 11 and 12 in this response and respectfully remind the Examiner that if a generic claim is found to be allowable, an additional number of species should be rejoined for examination in this application.

### **III. Rejection of Claims under 35 U.S.C. § 103(a)**

#### **A. Ramirez**

Claims 1-10 and 56-57 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over U.S. Patent No. 5,632,996 to Ramirez *et al.* (“Ramirez”). Applicants respectfully traverse the rejection.

Ramirez fails to render the claimed invention obvious because it does not teach or fairly suggest the following claim limitations: (i) that the benzoyl peroxide particles have an effective average particle size of less than about 2000 nm, and (ii) that the claimed composition comprises at least one surface stabilizer associated with the surface of the benzoyl peroxide particles.

#### **1. Ramirez Does Not Teach the Claimed Benzoyl Peroxide Particle Size**

Concerning limitation (i), the Examiner acknowledges that Ramirez “does not teach the specific particle size of the [benzoyl peroxide]” (final Office Action, page 7, line 5), but contends that “absent any teaching of criticality by the applicant concerning the particle size listed in claims 1 and 3 it would be *prima facie* obvious that one of ordinary skill in the art would recognize that the particle size in claims 1 and 3 is a result effective variable which is a matter of routine optimization” (*supra*, last five lines).

Contrary to the Examiner’s contention, the benzoyl peroxide particle size recited in claims 1 and 3 is critical to the claimed invention and cannot be achieved by “routine optimization.” The particle size of benzoyl peroxide is critical, because the nanoparticulate compositions of benzoyl peroxide possess a number of advantages over the conventional microparticles of benzoyl peroxide. These advantages flow as a direct result of the reduction in particle size of benzoyl peroxide. The exemplary advantages are discussed in the specification, paragraph [0026] bridging pages 8 and 9. For example, the benzoyl peroxide compositions of the invention, as compared to prior art non-nanoparticulate benzoyl peroxide compositions – such as

those described in Ramirez - may offer one or more of the following advantages: (1) faster onset of action; (2) a potential decrease in the frequency of dosing; (3) smaller doses of benzoyl peroxide required to obtain the same pharmacological effect; (4) improved performance characteristics, such as higher dose loading; (5) bioadhesive benzoyl peroxide formulations, which can coat the desired site of application and be retained for a period of time, thereby increasing the efficacy of the drug as well as eliminating or decreasing the frequency of dosing; (6) low viscosity liquid nanoparticulate benzoyl peroxide compositions, useful for topical application of liquid washes; (7) the nanoparticulate benzoyl peroxide compositions can be formulated in a dried form which readily redisperses, such as for reconstitution in a liquid to be used in a wash; (8) the nanoparticulate benzoyl peroxide compositions can be used in conjunction with other active agents; and (9) the nanoparticulate benzoyl peroxide compositions do not require organic solvents or pH extremes.

## **2. The Claimed Invention Demonstrates Unexpected Results**

Furthermore, the specification explicitly states that “not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition” (page 8, paragraph [0024]) and that “the choice of a surface stabilizer for benzoyl peroxide is non-trivial and required extensive experimentation to realize a desirable formulation” (page 17, paragraph [0065]). Accordingly, it is the surprising finding of the present inventors that benzoyl peroxide nanoparticulate compositions can be made. The additional art cited by the Examiner further attests to the point that benzoyl peroxide nanoparticulate compositions were not successfully made prior to the invention. For example, none of U.S. Patent No. 4,401,835 to Tarasov (“Tarasov”), U.S. Patent No. 4,917,816 to Self (“Self”), and U.S. Patent No. 5,662,883 to Bagchi et al. (“Bagchi”) discloses the claimed compositions comprising, *inter alia*, benzoyl peroxide particles having an effective average particle size of less than about 2000 nm. These cited references are further discussed below.

**3. The alkylbenzoate of Ramirez is not Equivalent to a Surface Stabilizer According to the Claimed Invention**

In relation to limitation (ii), the Examiner seems to incorrectly equate the surface stabilizers of the claimed invention with alkylbenzoate of Ramirez. First of all, the function of the surface stabilizers of the invention are to stabilize the nanoparticles of benzoyl peroxide by associating with the surface of the nanoparticles, such that “the benzoyl peroxide particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time,” “the physical structure of the benzoyl peroxide particles is not altered over time,” and “the benzoyl peroxide particles are chemically stable” (specification, page 10, paragraph [0034]).

In contrast, Ramirez discloses that alkylbenzoate, along with other benzoic acid esters, is used as a *solvent* to solubilize benzoyl peroxide crystalline material. See Ramirez, column 1, lines 61-67.

Second, Ramirez does not teach any of the surface stabilizers prescribed by claims 8, 10 and 12. Therefore, there is no evidence that the benzoic acid esters of Ramirez encompass the claimed surface stabilizers. Even armed with the teaching that benzoic acid esters can be used as a solvent, one skilled person would not have considered it obvious to use the surface stabilizers of the claimed invention to stabilize the nanoparticles of benzoyl peroxide.

Because Ramirez fails to meet either of the claim limitations, the obviousness rejection should be withdrawn.

**4. Tarasov, Bagchi, and Self do not Remedy the Deficiencies of Ramirez**

In addition, the Examiner cited Tarasov, Bagchi, and Self in response to Applicants’ arguments submitted on June 5, 2007. Because these references were not officially made of record in a PTO-892 form and because the Examiner did not rely on these references in the rejection rationale, Applicants presume that these references were applied to establish the state of art at the time of filing. In particular, the Examiner states that “the Examiner has included several applications

published before the Applicant's filing date that [that] enable one of ordinary skill in the art to make Benzoyl Peroxide crystals of extremely small size" (final Office Action, page 3, second paragraph). Nevertheless, as discussed below, none of these references serves the purpose intended by the Examiner.

For example, Tarasov teaches "a method for the preparation of benzoyl peroxide in crystalline form, which crystals may range in size below 10 microns" (abstract). Tarasov does not teach or suggest reducing the particle size of benzoyl peroxide to less than 2 microns (e.g., less than 2000 nm), nor does Tarasov teach the use of surface stabilizers to stabilize benzoyl peroxide nanoparticles, as recited in claim 1. Examples I & II of Tarasov further mention that the majority of the benzoyl peroxide granules have a size smaller than about 0.25 mm (column 5, lines 37-38), which is about 100-fold larger than the benzoyl peroxide particle size of the claimed composition.

Bagchi teaches a method for reducing particle size to the range between up to 10 nm and less than 400 nm. However, Bagchi does not specifically teach a nanocomposition of benzoyl peroxide but has a laundry list of the genera of chemical compositions (the paragraph bridging columns 5 and 6).

Self teaches a method for preparing benzoyl peroxide dispersions, where the particle size of benzoyl peroxide is less than 10 microns, or from about 2 to about 5 microns (column 9, lines 12-14). Self does not teach the claimed benzoyl peroxide compositions having an effective average particle size of less than about 2000 nm and a surface stabilizer associated with the surface thereof. Moreover, the Examiner's rejection is based on a factual error of equating the defoamer of Self with the surface stabilizers of the claimed invention (final Office Action, page 4, line 2). The surface stabilizers of the invention are discussed above. In contrast, Self explicitly states that a defoamer is included in the composition to reduce the incidence of foaming of the dispersion of benzoyl peroxide. One skilled in the art would not have considered it obvious to use the defoamer of Self as a surface stabilizer of the claimed invention.

**5. The Examiner has not met the Burden of Establishing a Rejection under the Obvious to Try Standard under Guidelines Established by *KSR***

The Examiner further states that “the teachings of these three references enable one of ordinary skill in the art to optimize the size of a benzoyl peroxide” (final Office Action, page 4, second paragraph).

To reject a claim based on an “Obvious to Try” standard – choosing from a finite number of identified, predictable solutions with a reasonable expectation of success, the Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, as published in the Federal Registrar/Vol. 72, No. 195/ Wednesday, October 10, 2007, require the Office Action to articulate the following:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.

As discussed in the specification, the predictability in the art is lacking, because “not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition,” and “it was surprisingly discovered that stable nanoparticulate benzoyl peroxide formulations can be made” (specification, page 8, paragraph [0024]). Therefore, in view of

unpredictability of the art, the Examiner has failed to establish a *prime facie* case of obviousness in accordance with the Examination Guidelines.

**B. Ramirez and Kanios**

Claims 1-10, 14-16 and 56-57 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Ramirez in view of U.S. Patent No. 5,719,197 to Kanios *et al.* (“Kanios”). Applicants respectfully traverse the rejection.

Ramirez is discussed *supra*. Kanios is cited for allegedly teaching bioadhesive carriers and additional active agents. However, Kanios does not remedy the deficiencies of the primary references by teaching a nanoparticulate composition of benzoyl peroxide having an effective particle size of less than 2000 nm, and a surface stabilizer associated with the surface thereof. Accordingly, the obviousness rejection should be withdrawn.

**C. Ramirez, Kanios, and Bartnick**

Claims 1-10, 13-17 and 56-57 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Ramirez in view of Kanios and U.S. Patent No. 5,399,35 to Bartnick *et al.* (“Bartnick”). Applicants respectfully traverse the rejection.

Ramirez and Kanios are discussed *supra*. Bartnick is cited for allegedly teaching the inclusion of antibiotics, lactic acid, PVP, lysozyme, etc. in a composition to disinfect undamaged skin. Bartnick is not even related to a nanoparticulate composition of benzoyl peroxide, and does not provide any teaching of benzoyl peroxide particles having an effective particle size of less than 2000 nm, or a surface stabilizer associated with the surface thereof. Thus, the combined teachings of all of the cited references fail to render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of the obviousness rejection.

CONCLUSION

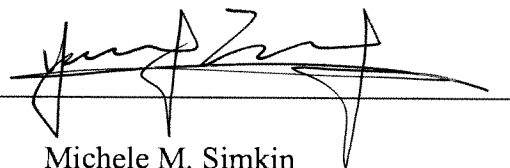
The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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